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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,428	01/23/2004	Laura Simmons	11669.120USU1	6080

23552 7590 09/11/2007
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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
09/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,428	SIMMONS, LAURA	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34,37-61,63-74 and 82-127* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34, 37-61, 63-74, and 82-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/9/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/15/07 has been entered.

2. Claims 1-34, 37-61, 63-74, and 82-127 are pending and are being acted upon in this Office Action.

3. The preliminary supplemental amendment filed on 8/31/07 was not entered because entry of the amendment would unduly interfere with the preparation of the Office action. See 37 CFR 1.115(b)(2). The examiner spent a significant amount of time on the preparation of an Office action before the preliminary amendment was received. On the date of receipt of the amendment, the examiner had completed the Drafting of the Office Action.

   Furthermore, entry of the preliminary amendment would require significant additional time on the preparation of the Office action. Specifically, entry of the preliminary amendment would require the examiner to revise the Office Action Extensively to address the new issue in the preliminary amendment. A responsive reply (under 37 CFR 1.111 or 37 CFR 1.113 as appropriate) to this Office action must be timely filed to avoid abandonment. If this is not a final Office action, applicant may wish to resubmit the amendment along with a responsive reply under 37 CFR 1.111 to ensure proper entry of the amendment.

4. Claims 14, 29, 49, 52-53, 63, 64, 92, 104, 117 and 122 are objected to because the plural "mixtures thereof" should have been singular "a mixture thereof".

5. Claim 6 is objected to because the phrase "wherein expressing a variable domain of the antibody or antigen binding fragment comprising at least one modified FR in a host cell comprises expressing a polynucleotide encoding the variable domain comprising at least one modified FR" is not concise. It is suggested that claim 6 be amended to recite "The

method of claim 1, wherein the host cell comprises a polynucleotide encoding said variable domain comprising at least one modified FR."

6. Claim 8 is objected to because the phrase "wherein the polynucleotide is comprised within an expression vector" could have been changed for a better phrase to reflect the claimed invention. For example, "wherein the host cell comprises an expression vector".

7. Claim 25 is objected to because "A method for preparing ... *antigen binding fragment*..." is missing the article "an", for example "A method for preparing ...*an* antigen binding fragment...". Further, the terms "FR", "HVR1" and "HVR2" at lines 4 and 5 that appear for the first time in an independent claim should have been spelled out, i.e., "framework region (FR)", "hypervariable region 1 (HVR1)" and "hypervariable region 2 (HVR2)", respectively.

8. Claim 33 is objected to because the phrase "wherein expressing comprises: expressing an expression vector comprising a polynucleotide encoding a variable domain comprising the HVR1 and/or HVR2 of the non-human antibody, and the selected FR" should have been "wherein the host cell comprises an expression vector comprising a polynucleotide encoding a variable domain comprising the HVR1 and/or HVR2 of the non-human antibody, and the selected FR".

9. Claim 44 is objected to because the phrase "wherein expressing comprises expressing an expression vector comprising a first polynucleotide that encodes a variable domain comprising the HVR1 and/or HVR2 amino acid sequence of the antibody or antigen binding fragment and at least one modified FR" should have been "wherein the host cell comprising an expression vector comprising a first polynucleotide that encodes a variable domain comprising the HVR1 and/or HVR2 amino acid sequence of the antibody or antigen binding fragment and at least one modified FR".

10. Claim 50 is objected to because "A method for preparing ... *antigen binding fragment*..." is missing the article "an", for example "A method for preparing ...*an* antigen binding fragment...". Further, the terms "HVR1" and "HVR2" at line 7 that appear for the first

time in an independent claim should have been spelled out, i.e., "hypervariable region 1 (HVR1)" and "hypervariable region 2 (HVR2)", respectively.

11. Claim 60 is objected to because "wherein the step of expressing comprises expressing an expression vector comprising a first polynucleotide that encodes the modified variable domain sequence with an amino acid substitution in at least one of the amino acids proximal to a cys residue, wherein at least one amino acid is substituted with the amino acid at the corresponding position in the selected subgroup consensus sequence." should have been "wherein the host cell comprising an expression vector comprising a first polynucleotide that encodes said modified variable domain sequence with an amino acid substitution in at least one of the amino acids proximal to a cys residue, wherein at least one amino acid is substituted with the amino acid at the corresponding position in the selected subgroup consensus sequence."

12. Claims 67 and 68 are objected to because it is the word "unmodified" is missing in "compared to the antibody or antigen binding fragment" in said claims at line 3.

13. Claim 82 is objected to because the terms "FR" at line 4, "HVR1" and "HVR2" at line 7 that appear for the first time in an independent claim should have been spelled out, i.e., "framework region", "hypervariable region 1 (HVR1)" and "hypervariable region 2 (HVR2)", respectively.

14. Claim 83 is objected to because the second "is" at line 2 is not necessary and is best to be deleted.

15. Claim 87 is objected to because "wherein expressing comprises expressing an expression vector comprising a first polynucleotide that encodes the variable domain comprising the HVR1 and/or HVR2 amino acid sequence and the modified FR" should have been "wherein the host cell comprises an expression vector comprising a first polynucleotide that encodes the variable domain comprising the HVR1 and/or HVR2 amino acid sequence and the modified FR".

16. Claim 101 is objected to because "wherein the polynucleotide molecule is comprised within an expression vector that comprises a polynucleotide molecule encoding the modified variable domain and at least one constant region domain operably linked to a promoter, a heat stable enterotoxin sequence that can direct secretion to the periplasm, and a terminator sequence" should have been "wherein the host cell comprising an expression vector that comprises a polynucleotide molecule encoding the modified variable domain and at least one constant region domain operably linked to a promoter, a heat stable enterotoxin sequence that can direct secretion to the periplasm, and a terminator sequence".

17. Claim 118 is objected to because "SEQ. ID NO: 1" should have been "SEQ ID NO: 1".

18. Claims 19-21, 42, 43, 52-54, 56-57, 63-64, 122, 123 and 124 are objected to under 37 CFR 1.821(d) because SEQ ID NO: is required.

19. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 1-34, 37-61, 63-74, and 82-127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "in high yield" in claim 1 is ambiguous and indefinite because the term "high yield" is a relative term. It is not clear to one of ordinary skilled in the art the metes and bound of the claimed invention.

The method steps in claim 1 are not in chronological order and not in active tense because of the wherein clause. It is suggested that claim 1 be amended to recite a method for improving the yield of antibody or antigen binding fragment thereof from a host cell, comprising the steps of: a) aligning the hypervariable region (HVR1)...b) selecting a human subgroup variable consensus sequence...c) identifying at least one amino acid position...d) substituting the amino acid at the corresponding position...e) expressing the antibody or antigen binding fragment comprising the variable domain comprising at least one modified framework region (FR) in the host cell, and f) recovering the antibody or

the antigen binding fragment thereof from the host cell, for example. This rejection applies equally to claims 25, 38, 39, 50, 71, 82, 96 and 100.

Claims 39 and 104 are incomplete for failing to achieve the goal set forth in the preamble. The missing steps are: expressing the modified framework region (FR) in the host cell, and recovering the antibody or the antigen binding fragment thereof from the host cell.

Claim 74 is incomplete because it is not clear the step of expressing said antibody or antibody fragment from i.e. host cell in vitro or in vivo.

Claims 19-21, 42, 43, 52-54, 56-57, 63-64, 122, 123 and 124 are ambiguous and indefinite because the reference sequence with sequence identifier (SEQ ID NO) for the stated positions to be substituted or modified is needed for said claims.

The remaining claims are rejected for depending from an indefinite claim.

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

22. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

23. Claims 25-31, 33, 36 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,884,879 (filed August 6, 1997; PTO 892).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35

U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are interpreted as a method of preparing a humanized antibody or antigen binding fragment by expressing said humanized antibody or antigen binding fragment thereof in host cell and recovering the humanized antibody or antigen binding fragment thereof from the host cell. This is because the wherein clause in the independent claims 25 and 71 is not an active step; the reference non-human antibody inherently has amino acid substitutions in the framework, HVR1 and/or HVR2 from human consensus sequences to form a humanized antibody or a binding fragment thereof.

The '879 patent teaches a method of preparing a humanized antibody or antigen binding fragment thereof wherein said antibody or antigen binding fragment thereof has the HVR1 amino acid sequence of GYTFTYGIN (reference SEQ ID NO: 110) or GYDFTHYGMN (reference SEQ ID NO: 128) which are identical to the claimed SEQ ID NO: 14 and SEQ ID NO: 18, respectively. The reference method for preparing humanized anti-VEGF antibody or antigen binding thereof by expressing said antibody having or antigen binding fragment thereof in host cell such as prokaryote *E coli* or mammalian host cell such as VERO or CHO cell (see col. 25 lines 126 through col. 26, in particular) and recovering said antibody or antigen binding fragment thereof (see col. 27, lines 35-61, in particular). The reference variable heavy chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup III (see col. 14, lines 34-67 through col. 15, lines 1-2, sequence alignment in Figure 1A, in particular). The reference variable light chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup I (see col. 15, lines 28-44, sequence alignment in Figure 1B, in particular). Thus the reference teachings anticipate the claimed invention.

24. Claims 25-31, 33, 36-37 and 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/45331 publication (published Oct 1998; PTO 1449).

The claims are interpreted as a method of preparing a humanized antibody or antigen binding fragment by expressing said humanized antibody or antigen binding

fragment thereof in host cell and recovering the humanized antibody or antigen binding fragment thereof from the host cell. This is because the wherein clause in the independent claims 25 and 71 is not an active step; the reference non-human antibody inherently has amino acid substitutions in the framework, HVR1 and/or HVR2 from human consensus sequences to form a humanized antibody or binding fragment thereof.

The WO 98/45331 publication teaches a method for preparing humanized antibody or antigen binding fragment thereof by expressing the humanized antibody or antigen binding fragment comprising the variable domain in host cell and recovering the reference humanized antibody (see entire document, abstract, page 25-26, page 37, in particular). The reference furthers the antibody variable domain cysteine residues not involved in maintaining the proper conformation of the humanized or variants thereof may also be substituted to improve oxidative stability and prevent aberrant crosslinking, see page 28, in particular). The reference method for preparing humanized anti-VEGF antibody or antigen binding thereof by expressing said antibody having or antigen binding fragment thereof in host cell such as prokaryote *E coli* or mammalian host cell such as VERO or CHO cell (see page 37, in particular) and recovering said antibody or antigen binding fragment thereof (see col. 38, in particular). The reference variable heavy chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup III (see page 61, in particular). The reference variable light chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup I (see page 61-63 in particular). The reference humanized antibody or antigen binding fragment thereof wherein said antibody or antigen binding fragment thereof has the GYDFTHYGMN (see page 74, Y0243-1, reference SEQ ID NO: 86) which is identical to the claimed SEQ ID NO: 18. Thus the reference teachings anticipate the claimed invention.

25. No claim is allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, PhD whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be

left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

27. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Patent Examiner
Technology Center 1600
August 31, 2007